CBER, Technology and Public Health: Looking Ahead

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Brief Outline

- **Provide updates on recent activities and accomplishments at CBER**
- **Commissioner and CBER priorities**
- **CBER Vision for the Future**
- **Public health, technology and management initiatives for 2004, including “Critical Path”**

Selected Accomplishments

- **Product Review/Approval: Met all PDUFA & MDUFMA Milestones**
  - ***Reinvention of device review and performance***
- **Public Health**
  - WNV Blood Donor Screening in 8 months
    - Unprecedented collaborative effort with blood, diagnostics industries, blood banks, academia and CDC
  - New HIV, hep C tests, TRANSNET Monitoring Pilot
  - Successful response to blood “white particles”, SARS, other EID events: outreach on product development
    - **SARS examples; working with CDC/NIH in assuring provision of suitable vaccine isolates of SARS coronavirus; testing viral inactivation methods and parameters**
  - Risk Assessment/Guidances re: TSE, CT, blood safety
  - New products, e.g. tD, Flumist vaccines, fibrin sealant, α-1 proteinase

Selected Accomplishments II

- **Counterterrorism**
  - Now ~ 25% of CBER effort/resource use
  - Proactive needs/gap assessments/inventories
  - Emergency availability of critical countermeasures for smallpox, botulinum and anthrax threats (vaccines/blood/immunoglobulins)
  - Critical participation in multiple Task Forces for and outreach re: Product Development including industry, CDC, NIH and DOD
  - Proactive site visits/manufacturers' assistance

Selected Accomplishments III

- **Patient Safety**
  - CMS and UHC Collaborations on vaccine/tissue safety
- **New Technologies**
  - Successful management of SCID/Gene Therapy events
  - BRMAC re: development of islet cell transplantation
  - Cellular protect CMCC reviewers guidance, vaccine cell substrate guidance
  - Major research on GT and xeno safety, stem cell characterization, CT products and assays
- **International Efforts**
  - Re-designated WHO Collaborating Center
  - WHO Guideline on Pre-clinical Vaccine Studies
  - Xeno and Gene Therapy outreach with WHO, others
  - Plasma derivative, thrombin outreach and standards

Selected Accomplishments IV

- **IT**
  - CBER Agency Leader in e submissions and secure digitally signed correspondence
  - 2003 Secretary's Award in e government
  - Gemcris: Secretary's Award (with NIH)
  - Under consolidated IT, Agency Lead for Gateway
- **Communications and Outreach:**
  - 2 million Web hits/month, 3 listservs
  - Rapid Dissemination of Critical Data: examples
    - **Outstanding responses to counterfeiting: e.g. Epogen/Procrit**
    - **Biologic Storage in Preparation for Hurricane Isabel**
    - **Alert on unlicensed flu vaccines/providers**

Other General Updates

- **Consolidation of "therapeutics"completed, ongoing collaboration**
  - **Formalized agreements on consultative review**
  - **Continue joint support/collaboration in scientific arenas**
  - **Continued CBER involvement/collaboration in issues of biologics manufacturing (e.g. validation, PAT), and science/policy**
- **Budget challenges for CBER**
  - **2004 and 2005 tight**
- **Commissioner's strong support going forward for CBER as a Center with key role in innovative products, counterterrorism and public health**

CBER PDUFA II Application Review Performance

Cohort Years FY 1998 - FY 2002

Performance Goals		PDUFA II									
		FY 1998		FY 1999		FY 2000		FY 2001		FY 2002*	
		Performance	Goal	Performance	Goal	Performance	Goal	Performance	Goal	Performance	Goal
BLAs	Standard: 10 months			**100%**	30%	**100%**	50%	**100%**	70%	**100%**	90%
	12 months	**100%**	90%	**100%**	90%	**100%**	90%	**100%**	90%		
	Priority: 6 months	**100%**	90%	**100%**	90%	**100%**	90%	**100%**	90%	**100%**	90%
Efficacy Supplements	Standard: 10 months			**100%**	30%	**100%**	50%	**100%**	70%	**83%**	90%
	12 months	**100%**	90%	**100%**	90%	**100%**	90%	**100%**	90%		
	Priority: 6 months	**100%**	90%	**100%**	90%	**100%**	90%	**100%**	90%	**100%**	90%
Manufacturing Supplements	Prior Approval: 4 months			**92%**	30%	**92%**	50%	**95%**	70%	**99%**	90%
	6 months	**99%**	90%	**100%**	90%	**94%**	90%	**96%**	90%		
	CBE and CBE-30: 6 months	**99%**	90%	**96%**	90%	**97%**	90%	**94%**	90%	**99%**	90%
Resubmissions	Class 1: 2 months	**100%**	30%	**100%**	50%	**100%**	70%	**100%**	90%	**100%**	90%
	4 months	**100%**	90%	**100%**	90%	**100%**	90%	**100%**	90%		
	Class 2: 6 months	**100%**	90%	**100%**	90%	**100%**	90%	**100%**	90%	**100%**	90%

* Performance percentages do not include submissions transferred to CDER that were pending on October 1, 2003. Dashes (--) indicate no submissions of this type or the goal date has not been reached.

CBER Review Performance
FY 2003 Cohort of User Fee Applications

Application Types	Numbers				Percent of Actions*	
	Submitted	Filed	AP	RTF, UN, or WF	Within Goal	Overdue
New Products	8	8	2	0	100%	0%
Effectiveness Supplements	16	15	4	1	100%	0%
Manufacturing Supplements	903	897	656	6	99%	1%

***Submissions pending action as of October 1, 2003 and transferred to CDER are included in CBER receipts but not final actions. The CBER percentages in this report do not include transferred pending numbers.**

AP=Approved, RTF=Refuse To file, UN=Unacceptable For Filing, WF=Withdrawn Before Filing

Data as of 31-Mar-2004
(270bp)RIMS:04/15/04

CBER PDUFA III Application Review Performance

Cohort Years FY 2003 - FY 2007

Performance Goals		PDUFA III									
		FY 2003*		FY 2004		FY 2005		FY 2006		FY 2007	
		Performance	Goal	Performance	Goal	Performance	Goal	Performance	Goal	Performance	Goal
BLAs	Standard: 10 months	100%	90%	100%	90%	--	90%	--	90%	--	90%
	Priority: 6 months	100%	90%	--	90%	--	90%	--	90%	--	90%
Efficacy Supplements	Standard: 10 months	100%	90%	100%	90%	--	90%	--	90%	--	90%
	Priority: 6 months	100%	90%	--	90%	--	90%	--	90%	--	90%
Manufacturing Supplements	Prior Approval: 4 months	99%	90%	100%	90%	--	90%	--	90%	--	90%
	CBE and CBE-30: 6 months	99%	90%	100%	90%	--	90%	--	90%	--	90%
BLA Resubmissions	Class 1: 2 months	100%	90%	--	90%	--	90%	--	90%	--	90%
	Class 2: 6 months	100%	90%	--	90%	--	90%	--	90%	--	90%
Efficacy Supplement Resubmissions	Class 1: 2 months	100%	30%	--	50%	--	70%	--	80%	--	90%
	Class 1: 4 months			--	90%	--	90%	--	90%		
	Class 1: 6 months	100%	90%								
	Class 2: 6 months	100%	90%	--	90%	--	90%	--	90%	--	90%
Review Notifications	1st Cycle: 74 days	100%	50%	--	70%	--	90%	--	90%	--	90%

* Performance percentages do not include submissions transferred to CDER that were pending on October 1, 2003. Dashes (--) indicate no submissions of this type or the goal date has not been reached

Data as of 31-March-2004

(275bp)RIMS:4/15/2004

CBER PDUFA III Procedural Goals Performance

Cohort Years FY 2003 - FY 2007

Performance Goals	FY 2003*,**		FY 2004*		FY 2005		FY 2006		FY 2007	
	Performance	Goal	Performance	Goal	Performance	Goal	Performance	Goal	Performance	Goal
Meeting Management										
Respond to Meeting Request: 14 days	**98%**	90%	**98%**	90%	--	90%	--	90%	--	90%
Meeting Held: 30, 60, 75 days	**99%**	90%	**93%**	90%	--	90%	--	90%	--	90%
Minutes Finalized: 30 days	**98%**	90%	**97%**	90%	--	90%	--	90%	--	90%
Special Protocol Question Requests										
Assessment: 45 days	**100%**	90%	**100%**	90%	--	90%	**100%**	90%	--	90%
Major Dispute Resolution										
Respond to Request: 30 days	**100%**	90%	**100%**	90%	--	90%	**100%**	90%	--	90%
Clinical Holds										
Respond to Complete Response: 30 days	**97%**	90%	**95%**	90%	--	90%	**92%**	90%	--	90%

***Percentages are for requests for which the goal date has been reached; "--" means no requests have been received yet.**

****Percentages for FY 2003 do not include OTRR/ODEVI requests pending as of October 1, 2003**

*Data through 3/31/04

(274bp)RIMS:4/15/2004

Effort and Expertise in the Reinvention of CBER Device Management and MDUFMA

- CBER has substantially (~ 25%) increased device related effort in the last year
- In addition to increased device effort from employees, new hiring has allowed recruitment of individuals with specialized experience/expertise and diverse backgrounds - examples
  - reviewers with specific device/device related software experience (1 from industry, 1 IT)
  - RPMs with industry manufacturing experience
  - reviewers with clinical/academic experience in blood banking, transfusion medicine, apheresis

CBER Device Application Receipts
FY 2002 – FY 2004*

		MDUFMA	
	FY02	FY03	FY04*
PMAs (Traditional)	0	0	0
PMAs (Modular)	1	3	0
PMSs (180 Day)	5	3	2
510(k)s (All Types)	40	65	24
BLAs (Original)	2	0	1
BLSs (Efficacy)	0	3	0
BLSs (Manuf, PAS)	35	75	5

* FY 04 numbers for first four months - as of January 31, 2004

CBER 510k Review Time Performance
Receipt to Final Action
FY 2002-FY2004*

		MDUFMA	
	FY02	FY03	FY04*
CBER Review Time (days)	119.1	57.6	58.7
Average Number of Cycles	1.7	1.3	1.1

Includes SEs/NSEs/WDs

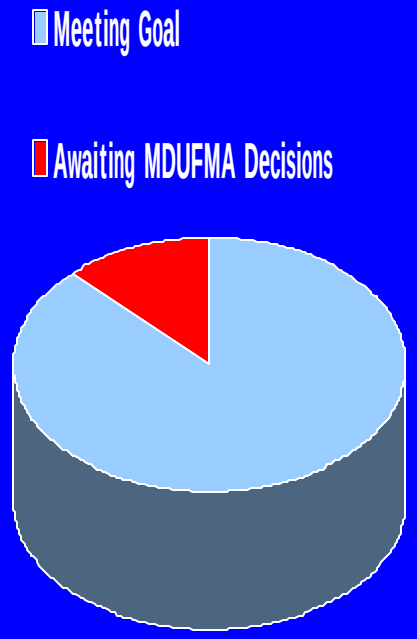
*FY 04 data for first four months through January 31, 2004

Performance Updates for MDUFMA

510(k) Applications

Goal: Decision within 90 total FDA days

	1st QTR FY 03	2nd QTR FY 03	3rd QTR FY 03	4th QTR FY 03	Annual Totals FY 03
Total Received	20	14	12	19	65
Total Filed	20	14	12	19	65
Meeting Goal	20	14	11	12	57 (88%)
Not Meeting Goal	0	0	0	0	0
Awaiting MDUFMA Decision	0	0	1	7	8 (12%)



FY 2003 Cohort

(as of 1/31/04)

Selected 2003-4 Device Approvals

- OraSure OraQuick Rapid HIV-1 Antibody Test
- MedMira Rapid HIV Test
- Ortho ProVue, Software Version 2.10,
- Vironostika HIV-1 Plus O Microelisa System
- ORTHO HbsAG ELISA Test System 3
- Aldecount Progenitor Cell Enumeration Kit
- *Future device needs and promise:*
  - Cell therapies and tissue engineering
  - Emerging infectious disease testing
  - Delivery systems for cells, vaccines, gene therapies and more

West Nile Update

- GenProbe and Roche NAT INDs
- ~ 6.4 million units tested in 2003!
  - Mostly as minipools (MP), targeted single donor NAT in highest incidence areas/periods
- ***>1000 WNV + donations intercepted and removed before transfusion***
  - Up to 20% of very low positive units may not be detected by mini-pooled (MP) NAT, few documented infections, studies in progress
- A major public health success achieved through proactive partnering, guidance and efforts of diagnostics & blood industries, CDC and FDA

FDA's Strategic Plan

- Science Based Risk Management
- Better Informed Consumers
- Patient Safety
- Counter-terrorism
- Strong FDA
  - Personnel, processes, infrastructure

All highly pertinent to CBER and our products & CBER actions will support Plan.

Additional CBER Cross-Cutting Priority Approaches to FDA Goals

- ***Enhance outside collaboration & input ; "outside in" & "inside out"; e.g. sabbaticals, clinical practice, blood banking program***
- ***Strengthen the base for & performance of CBER and collaborative science & review***
  - ***Includes epidemiologic, clinical and risk sciences and cutting across product and expertise areas***
    - ***E.g. CBER Grand Rounds***
  - **Focus on stumbling blocks on "critical path" to product development and new technologies – more later**
  - Enhanced interactions, collaboration and leveraging with NIH, other regulatory authorities and other partners
  - Continue increases in transparency, input, tracking, focus and review.
- ***Strengthen emergency response/crisis management***

Vision for CBER

INNOVATIVE TECHNOLOGY ADVANCING PUBLIC HEALTH

- ***Protect and improve public and individual health in the US and, where feasible, globally***
- ***Facilitate the development, approval and access to safe and effective products and promising new technologies***
- ***Strengthen CBER as a preeminent regulatory organization for biologics***

CBER 2004: New Initiatives

- **Efficient Risk Management**
  - **Enhanced Review Management and Processes**
    - ***Review Template Initiative***
      - *Enhance consistency, quality of review and submissions as well as facilitating electronic processes*
    - **Review of Review Initiative**
      - *Identify best practices/management and prepare for Agency-wide quality initiatives*
  - **GMPs for 21st Century**
    - **CBER serves on Steering Committee**
    - **CBER already had adopted many "new" practices**
      - **E.g.: scientists/clinicians on inspections, specialized teams and training, risk based prioritization, Center review of warning letters**
      - **Additional Center Initiative: enhance inspectional integration/coordination with product review process**

CBER 2004: New Initiatives II

- Better Informed Consumers
  - **CBER Communication Strategic Plan**
  - ***"CBER Communicates":*** enhance CBER communication to health care consumers through appropriate media at appropriate health literacy levels

CBER 2004: Major Initiatives III

- Patient Safety
  - Tissue Safety System
    - Finalization of Donor Suitability & Good Tissue Practice Rules
    - Creation of *Tissue Safety Team*
      - Interdisciplinary: OCTGT, OBE, OCBQ, OITM
      - Active Surveillance
      - Adverse Event Reports and Analysis
      - Training, outreach, inspection and compliance

CBER 2004: Major New Initiatives IV

- Counterterrorism
  - Bioshield related guidance and evaluation
  - New technologies
    - E.g. platform technologies for vaccines and diagnostics (critical path initiative)
  - *CT Product Safety Plan*
    - Defined measures to reduce potential vulnerabilities of CBER biologic products essential to the response to terrorist events

CBER 2004: Major Initiatives V

- Strong FDA
  - ***Management Training Initiative***
  - ***Risk Assessment, Management and Communication Training for Reviewers***
  - External review/input re: broad scientific programs, needs and opportunities
  - ***Global Strategic Plan***
    - possible Global Vaccine Assistance Pilot Program (GVAP)

- Cross- Cutting Initiative:

  Emerging Infectious Diseases

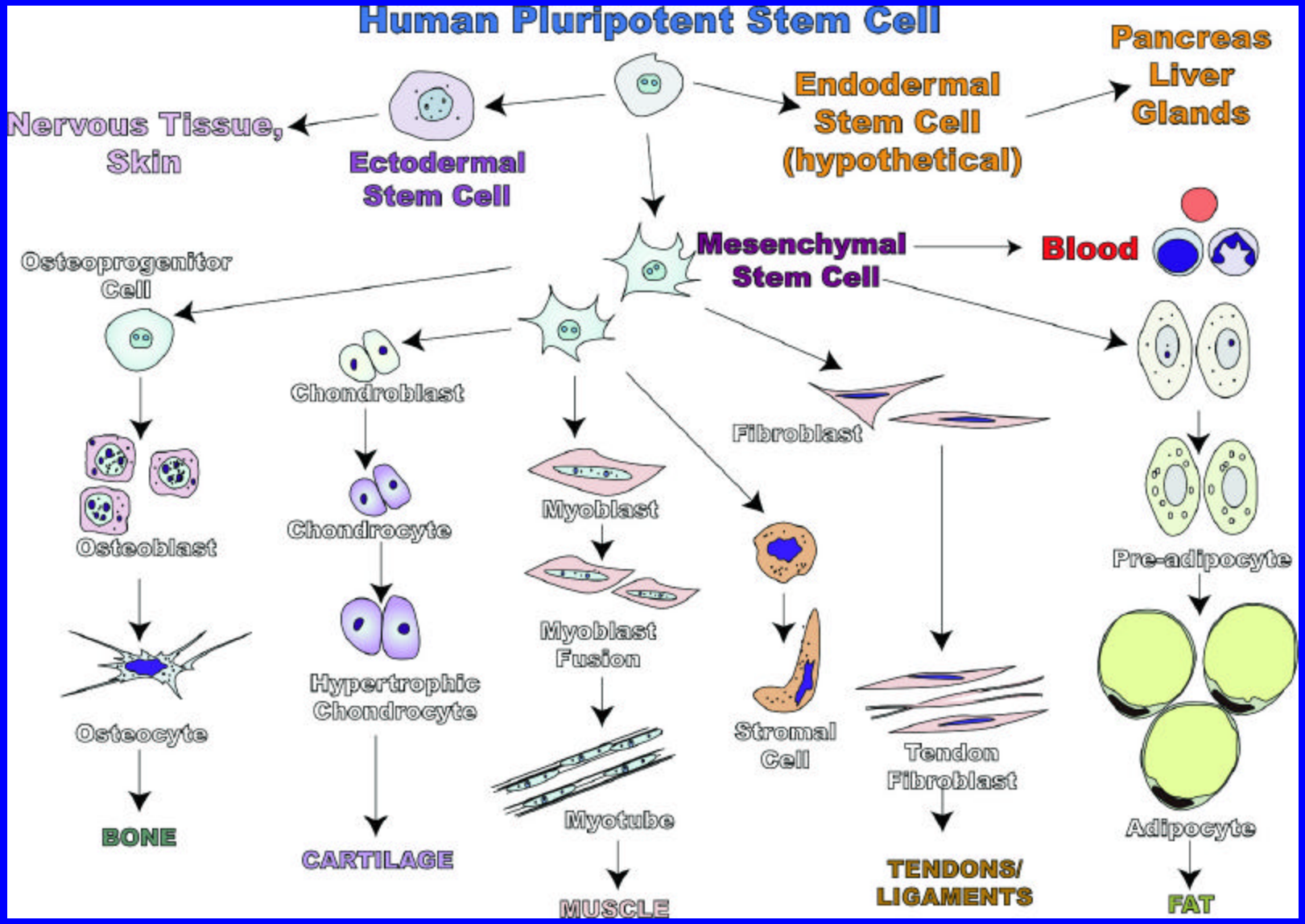
  - ***Products for prevention, treatment, diagnosis***
  - ***Protection of blood, cell, vaccine and tissue safety***

FDA Critical Path Initiative

- **Facilitate product development through better tools and latest technologies for safety, efficacy and product manufacturing**
  www.fda.gov/oc/initiatives/criticalpath/whitepaper.
- **Focus intramural and extramural science as resources permit**
  - **Includes identifying areas, especially new technologies, where needed standards, methods, assays, guidance can be helpful**
    - » ***(e*.g. gene therapy, tissue engineering, stem cells, new vaccine technologies, blood "substitutes", pathogen inactivation & detection)**
  - **Assure internal expertise, appropriate partnerships with industry, academic/scientific community and consumers**
  - **Identify "roadblocks", scientific and regulatory, and develop appropriate solutions – e.g. VIG potency assay, rapid bacterial testing methods**
  - **Guidance, standards, outreach, creative approaches to product development, safety/efficacy assessment and review**

Examples of Opportunities with CBER Products

- New vaccine delivery systems, rapid use vectors
- Develop and make available well characterized cell banks (and related methods to assay for safety/adventitious agents) useful for vaccine and other biologics production
- Characterization of cell therapies & links to standardized outcomes (e.g. HPSCs)
- Methods & validation of pathogen inactivation for blood, plasma, tissues and other products
- Multipathogen and rapid detection methodologies for biologics including blood and tissue products
- Improving longevity/storage of blood and tissues

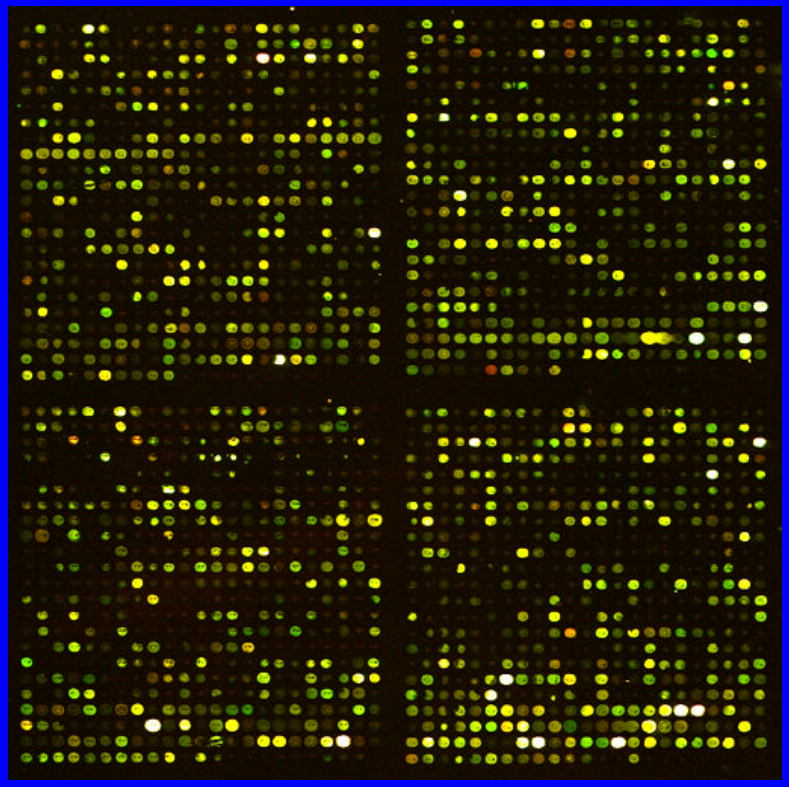

Human Pluripotent Stem Cell
Nervous Tissue, Skin
Ectodermal Stem Cell
Endodermal Stem Cell (hypothetical)
Pancreas
Liver
Glands
Mesenchymal Stem Cell
Blood
Osteoprogenitor Cell
Osteoblast
Osteocyte
BONE
Chondroblast
Chondrocyte
Hypertrophic Chondrocyte
CARTILAGE
Myoblast
Myoblast Fusion
Myotube
MUSCLE
Fibroblast
Stromal Cell
Tendon Fibroblast
TENDONS/ LIGAMENTS
Pre-adipocyte
Adipocyte
FAT

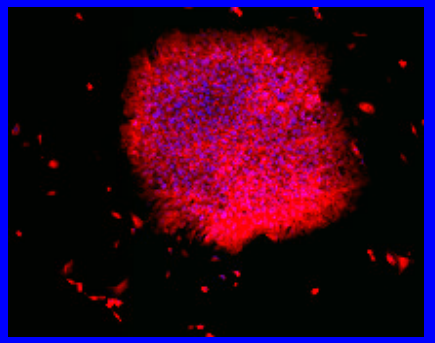
Characterization of Stem Cells to Assure Safety & Effectiveness

- Normal stem cells can form a variety of tissues and cell types, including blood, brain, bone, muscle etc.
- Safety concerns exist that include:
  - Risk of unregulated growth after inoculation (cancer)
  - Contamination with infectious agents
- Characterization of the stem cells is important in regulating their use as a medical therapy
  - Inoculated in or expanded from one form, change to another state
- Need novel technological methods for accurate characterization

Quality Assessment of Stem Cells by Gene Expression Profile Microarray

CBER scientists have developed a method to identify and characterize 86 common "stemness" genes in 6 stem cell lines





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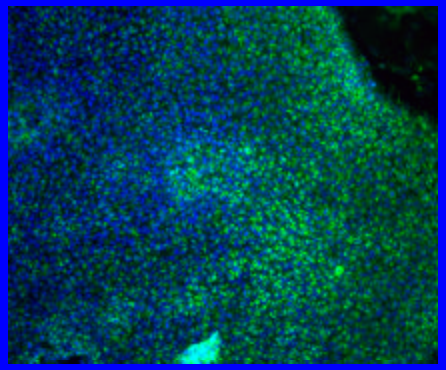

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Stem Cells as Medical Therapy

- Microarrays being used to:
  - **Identify connection between specific stem cell and developmental pathway to specific tissue**
  - **Identify contamination of stem cells with other cells or infectious agents**
  - **Identify stem cells with higher than acceptable risk of developing into cancerous cells**
  - **Link to standardized and measurable outcomes:**
    - ***Types and gene expression patterns of stem cells that will predictably and reproducibly perform well as medical therapy***

Thanks!

- We are very proud of CBER and its mission
- Both traditional & cutting edge products and technologies offer tremendous promise to protect and enhance health
- Despite and because of change and challenges, we see a bright and promising future.
- We seek and need your input and increased engagement, now and in the future.

CBER:

INNOVATIVE TECHNOLOGY ADVANCING PUBLIC HEALTH